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Efficacy and Safety of Torcetrapib, a Novel Cholesteryl Ester Transfer Protein Inhibitor, in Individuals With Below-Average High-Density Lipoprotein Cholesterol Levels on a Background of Atorvastatin

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OBJECTIVES This study sought to evaluate the efficacy and safety of torcetrapib in patients with low high-density lipoprotein cholesterol (HDL-C) levels receiving background atorvastatin.

BACKGROUND Elevating HDL-C levels may reduce the residual cardiovascular risk that is observed in patients treated with statin therapy. Torcetrapib (a cholesteryl ester transfer protein inhibitor) increases HDL-C and decreases low-density lipoprotein cholesterol (LDL-C).

METHODS This was a multicenter, double-blind, randomized trial. Patients with below-average HDL-C (men <44 mg/dl; women <54 mg/dl) who were eligible for statin therapy according to National Cholesterol Education Program Adult Treatment Panel III guidelines or who had LDL-C >130 mg/dl at screening entered an 8-week run-in period with atorvastatin 20 mg/day before randomization (n = 174) to torcetrapib 10, 30, 60, or 90 mg/day or placebo for 8 weeks. Atorvastatin was continued during treatment with torcetrapib.

RESULTS After 8 weeks, the percent change from baseline with torcetrapib (least-squares mean difference from placebo) ranged from 8.3% to 40.2% for HDL-C ($p \leq 0.0001$ for 30-mg and higher doses) and from 0.6% to −18.9% for LDL-C ($p < 0.01$ for 60-mg and 90-mg doses). Particle size for both HDL and LDL increased with torcetrapib. The incidence of all-causality and treatment-related adverse events was similar across placebo and torcetrapib treatment groups with no evidence of a dose-related response. In some treatment groups, small increases in systolic and diastolic blood pressures were noted.

CONCLUSIONS In statin-eligible patients, torcetrapib plus background atorvastatin resulted in substantial, dose-dependent increases in HDL-C, accompanied by additional decreases in LDL-C beyond those seen with atorvastatin alone. Torcetrapib plus atorvastatin was generally well tolerated. (J Am Coll Cardiol 2006;48:1782–90) © 2006 by the American College of Cardiology Foundation

Lowering low-density lipoprotein cholesterol (LDL-C) levels is the primary focus of guidelines for the management of cardiovascular disease (CVD) (1,2). Statins are the drugs of choice for decreasing LDL-C and have shown large reductions in cardiovascular events in CVD prevention trials (3). Recent data also confirm that aggressive versus more moderate lipid-lowering therapy with statins is associated with greater benefits (4–6).

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Despite the impressive benefits of statins, it is apparent that even intensively treated patients retain a residual risk of cardiovascular events. In the PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial, in which patients with acute coronary syndromes were randomized to either moderate therapy with pravastatin 40 mg/day or intensive therapy with atorvastatin 80 mg/day, cardiovascular event rates were still 26.3% and 22.4%, respectively, after 2 years (6). Similarly, in the TNT (Treating to New Targets) trial, which also evaluated the benefits of intensive (atorvastatin 80 mg/day) versus more moderate (atorvastatin 10 mg/day) therapy, but in patients with stable rather than unstable coronary heart disease, a significant proportion of each treatment group experienced major vascular events after 5 years (8.7% vs. 10.9% with atorvastatin 80 mg and 10 mg, respectively) (5).

Reducing the residual cardiovascular risk in statin-treated patients may be achieved by complementing statin therapy with strategies targeting other components of the dyslipidemic state. As shown by the ARBITER (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol) 2 trial, one promising strategy may be to

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Abbreviations and Acronyms

AE	= adverse event
apo	= apolipoprotein
CETP	= cholesteryl ester transfer protein
CVD	= cardiovascular disease
DBP	= diastolic blood pressure
HDL-C	= high-density lipoprotein cholesterol
LDL-C	= low-density lipoprotein cholesterol
LS	= least-squares
NMR	= nuclear magnetic resonance
SBP	= systolic blood pressure
ULN	= upper limit of normal
VLDL-C	= very low-density lipoprotein cholesterol

elevate high-density lipoprotein cholesterol (HDL-C) levels. In the ARBITER 2 trial, addition of extended-release niacin to statin therapy increased HDL-C by 21% and slowed the progression of atherosclerosis (as measured by change in carotid intima-media thickness) compared with statin therapy alone in patients with known coronary heart disease and moderately low HDL-C levels (7).

One approach for elevating HDL-C is via the inhibition of cholesteryl ester transfer protein (CETP) (8). As described in an accompanying article (see pages 1774–1781 in this issue of the *Journal*), torcetrapib is a novel CETP inhibitor that substantially elevates HDL-C, modestly decreases LDL-C, and increases lipid particle size. The phase 2 study reported here provides additional data on the efficacy and safety of torcetrapib when administered on a background of atorvastatin to patients with a low level of HDL-C.

METHODS

Study design. This was a multicenter study (23 centers). After screening, participants entered an 8-week run-in period during which they received atorvastatin 20 mg/day. The HDL-C levels were verified during this run-in period. Eligible participants were then randomized to 8 weeks of double-blind treatment with either placebo or torcetrapib 10, 30, 60, or 90 mg once daily (Fig. 1). Atorvastatin therapy was continued during double-blind treatment.

Participants. Adults ages 18 to 65 years with low HDL-C levels (<44 mg/dl for men and <54 mg/dl for women) (9) were enrolled. Patients were also required to be on statin therapy or to have an LDL-C level >130 mg/dl. Exclusion criteria included an LDL-C level of ≥190 mg/dl or triglycerides ≥400 mg/dl, concomitant therapy with known lipid-altering effects on HDL-C (other than statins) within 30 days of screening, and major and/or unstable concurrent illnesses.

The protocol was approved by the institutional review board or independent ethics committee at each site and was conducted in compliance with the Declaration of Helsinki.

Lipid assessments. The primary end point was the percent change from baseline in HDL-C after 8 weeks. Absolute change from baseline in HDL-C and percent change and absolute change from baseline in LDL-C, triglycerides, and total cholesterol were secondary end points. Additional lipid analyses included apolipoprotein concentrations; HDL particle type; HDL, very low-density lipoprotein (VLDL), and LDL subclass composition; phospholipid concentrations; and nuclear magnetic resonance (NMR) lipoprofile.

Analytical methods. Biochemical analyses were performed by Medical Research Laboratories (Highland Heights, Kentucky). Total cholesterol and net triglycerides were quantified by a Centers for Disease Control and Prevention–standardized enzymatic assay in an automated chemistry analyzer. The HDL-C was measured by separating HDL from LDL and VLDL by heparin/$MnCl_2$ chemical precipitation. The LDL-C and VLDL cholesterol (VLDL-C) were estimated using the Friedewald formula (10). If total triglycerides were >400 mg/dl, LDL-C and VLDL-C were measured directly by β-quantification using ultracentrifugation. Phospholipid was measured by an automated enzy-

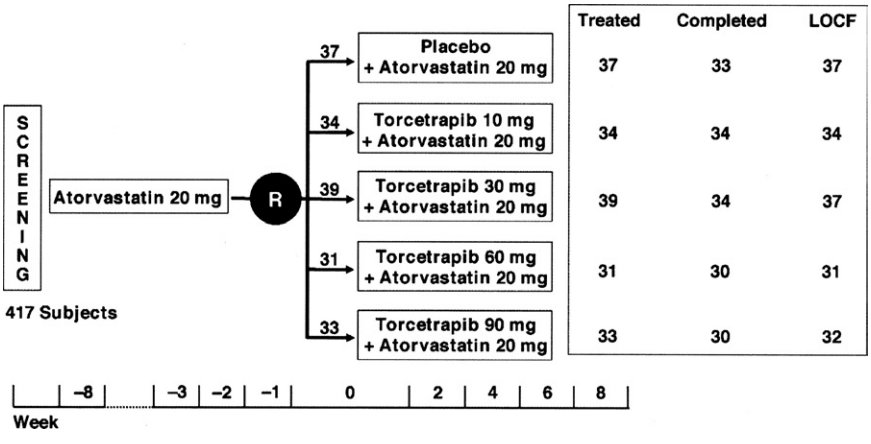

Figure 1. Schematic representation of study design and numbers of patients. At screening, patients were required to: 1) have a high-density lipoprotein cholesterol (HDL-C) level <44 mg/dl for men and <54 mg/dl for women, and 2) be on statin therapy or have a low-density lipoprotein cholesterol (LDL-C) level >130 mg/dl. A total of 69 patients were already receiving statin therapy at screening. Sample size was calculated based on earlier torcetrapib studies, with 25 patients per group yielding 80% power to detect a 25% treatment difference in HDL-C, assuming a common standard deviation of 30.5% and 2-sided *t* test with 5% type I error. LOCF = last observation carried forward (i.e., patients with baseline plus 1 post-baseline HDL-C measurement); R = randomization.

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Table 1. Baseline Patient Demographics and Lipid Parameters (All Subjects Received Background Atorvastatin 20 mg/day)

		Torcetrapib (mg/day)			
	Placebo	**10**	**30**	**60**	**90**
Demographics					
n	37	34	39	31	33
Men, n (%)	25 (68)	25 (74)	31 (79)	25 (81)	23 (70)
Mean age, yrs (±SD)	50 (±9)	49 (±9)	49 (±9)	49 (±8)	49 (±8)
Men	50 (±10)	49 (±9)	49 (±9)	48 (±8)	48 (±7)
Women	52 (±7)	49 (±11)	50 (±9)	54 (±6)	51 (±11)
Race or ethnicity, n (%)					
White	28 (75)	27 (79)	34 (87)	22 (71)	22 (67)
Black	1 (3)	1 (3)	1 (3)	2 (6)	2 (6)
Asian	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Hispanic	6 (16)	6 (18)	4 (10)	7 (23)	8 (24)
Other	1 (3)	0 (0)	0 (0)	0 (0)	1 (3)
Mean BMI, kg/m^2					
Men	29.5	29.7	30.3	30	28.9
Women	28.9	32.6	33.5	29.5	27.9
Mean SBP/DBP, mm Hg	118.5/77.7	120.7/76.9	117.1/75.1	119.4/79.4	121.4/78.8
Lipid parameters					
n	37	34	37	31	32
Mean HDL-C, mg/dl (±SD)*	40 (±6)	39 (±6)	39 (±7)	40 (±6)	42 (±6)
% <40 mg/dl	62	56	59	58	41
Mean LDL-C, mg/dl (±SD)*	88 (±20)	84 (±22)	85 (±17)	83 (±19)	89 (±17)
% <130 mg/dl	100	94	97	97	100
Mean TGs, mg/dl (±SD)*	170 (±75)	176 (±71)	163 (±70)	165 (±67)	151 (±63)
% <150 mg/dl	41	41	51	45	66
Mean TC, mg/dl (±SD)*	162 (±27)	158 (±25)	157 (±22)	155 (±19)	161 (±24)
% <200 mg/dl	95	91	97	100	91
Ratio of LDL-C to HDL-C (±SD)*	2.3 (±0.6)	2.1 (±0.5)	2.2 (±0.6)	2.1 (±0.6)	2.2 (±0.6)

*Baseline values are the measurements taken at the end of the atorvastatin run-in period.
BMI = body mass index; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; TGs = triglycerides.

matic colorimetric method. The HDL subclasses (HDL2 and HDL3) were separated by zonal ultracentrifugation. Apolipoprotein (apo) A-I, A-II, and B-100 were analyzed by an automated immunoturbidimetric procedure. Lipoprotein subclasses were determined using proton NMR by Liposciences (Raleigh, North Carolina) (11).

Safety assessments. Safety assessments included a physical examination and measurement of vital signs, electrocardiograms, and standard laboratory safety tests. Adverse events (AEs) were recorded.

Statistical analyses. The primary statistical analysis for efficacy included all randomized participants who received at least 1 dose of study treatment with at least 1 pretreatment and post-treatment end point measurement using the last-observation-carried-forward approach. The analysis of the primary end point (HDL-C percent change from baseline at week 8) used analysis of covariance using a linear model that included a term for treatment group and baseline value as a continuous covariate (SAS Proc Mixed using SAS version 6.12; SAS Institute Inc., Cary, North Carolina). Study center was not included as an independent variable. Least-squares (LS) means were computed, and pairwise treatment comparisons of torcetrapib dose group versus placebo (on a background of atorvastatin) were assessed for statistical significance at the $p = 0.05$ level (2-sided) using a step-down procedure to preserve the type 1 error across the multiple comparisons (12). A 95% confidence interval, unadjusted for multiplicity, was calculated for each pairwise comparison. Similar analyses were performed for secondary end points.

For lipid assessments, results are presented in figures as raw means for each time point. The percent changes in lipids at 8 weeks used for hypothesis testing are presented in tabular form.

For vital signs, each patient's post-baseline observations were averaged and a change from baseline was calculated. This measure was then analyzed in a manner analogous to the efficacy parameters previously discussed (i.e., analysis of covariance using SAS Proc Mixed with a linear model. including a term for treatment group and baseline value as a continuous covariate). The LS means were calculated, and 95% confidence intervals were computed for the within-treatment group change from baseline.

RESULTS

Baseline demographics. Baseline demographic characteristics and lipid profiles of the randomized participants (n = 174) were well balanced across treatment groups (Table 1). Mean HDL-C levels across treatment groups ranged from 39 to 42 mg/dl. Between 41% and 62% of the individuals in each group had HDL-C levels <40 mg/dl. Predictably, given the atorvastatin run-in period, the proportion of

Table 2. Change in Standard Lipid Parameters (All Subjects Received Background Atorvastatin 20 mg/day)

Mean Values at Baseline and Week 8 (Baseline, Final mg/dl)					
		Torcetrapib (mg/day)			
Lipid Parameter	Placebo	10	30	60	90
HDL-C	40, 40	39, 43	39, 49	40, 53	42, 60
LDL-C	88, 91	84, 86	85, 90	83, 74	89, 75
Triglycerides	170, 165	176, 178	163, 175	165, 169	151, 141
Total cholesterol	162, 164	158, 165	157, 174	155, 160	161, 162
LDL-C/HDL-C ratio	2.3, 2.3	2.1, 2.0	2.2, 1.9	2.1, 1.5	2.2, 1.4
Apo B-100/apo A-I ratio	0.8, 0.8	0.8, 0.7	0.8, 0.7	0.7, 0.7	0.8, 0.6

Percent Change From Baseline at Week 8 (LS Mean Differences Relative to Placebo Using LOCF Approach)				
	Torcetrapib (mg/day)			
Lipid Parameter	10	30	60	90
HDL-C (95% CI)	8.3 (−0.2, 16.9)	23.8‡ (15.4, 32.2)	33.1‡ (24.3, 41.9)	40.2‡ (31.3, 49.1)
LDL-C (95% CI)	0.6 (−8.9, 10.1)	2.7 (−6.6, 12.0)	−15.7† (−25.5, −6.0)	−18.9† (−28.5, −9.3)
Triglycerides (95% CI)	2.1 (−13.1, 17.3)	7.9 (−7.0, 22.8)	5.0 (−10.6, 20.6)	−12.3 (−27.8, 3.2)
Total cholesterol (95% CI)	3.0 (−2.8, 8.8)	9.1 (3.4, 14.8)	1.3 (−4.7, 7.2)	−0.2 (−6.1, 5.7)
LDL-C/HDL-C ratio (95% CI)	−7.1 (−18.5, 4.3)	−15.8† (−26.9, −4.7)	−31.8‡ (−43.5, −20.1)	−39.8‡ (−51.4, −28.3)
Apo B-100/apo A-I ratio (95% CI)	−4.2 (−15.3, 6.9)	−10.3 (−21.0, 0.52)	−13.5* (−24.8, −2.2)	−25.1‡ (−36.3, −13.9)

*$p < 0.05$. †$p < 0.01$. ‡$p \leq 0.0001$.
apo = apolipoprotein; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LOCF = last observation carried forward; LS = least-squares.

patients in each group with LDL-C levels <130 mg/dl ranged from 94% to 100%.

Efficacy—lipid parameters. Generally, the pattern of changes in the levels of HDL-C, LDL-C, and their respective apolipoproteins in this study of torcetrapib administered on a background of atorvastatin 20 mg/day to patients with below-average HDL-C levels was similar to that observed in a study of torcetrapib administered alone to an equivalent cohort of patients (see accompanying article, pages 1774–1781 in this issue of the *Journal*).

HDL AND HDL-RELATED APOLIPOPROTEINS. Torcetrapib on a background of atorvastatin dose-dependently increased HDL-C levels (Table 2, Fig. 2). Percent changes in HDL-C from baseline to week 8 ranged from +8.3% to +40.2% with torcetrapib 10 to 90 mg/day (LS mean difference from placebo). Differences were significant at doses of 30 mg and above ($p \leq 0.0001$). In each torcetrapib treatment group, increases in HDL-C levels were accompanied by increases in apo A-I and apo A-II levels (Table 3).

Ultracentrifugation/precipitation analysis indicated that torcetrapib on a background of atorvastatin increased levels of larger HDL particles (Table 3). The NMR spectroscopy confirmed these findings. At the 60-mg and 90-mg doses of torcetrapib, large HDL (8.3 to 13 nm) increased from 14.9

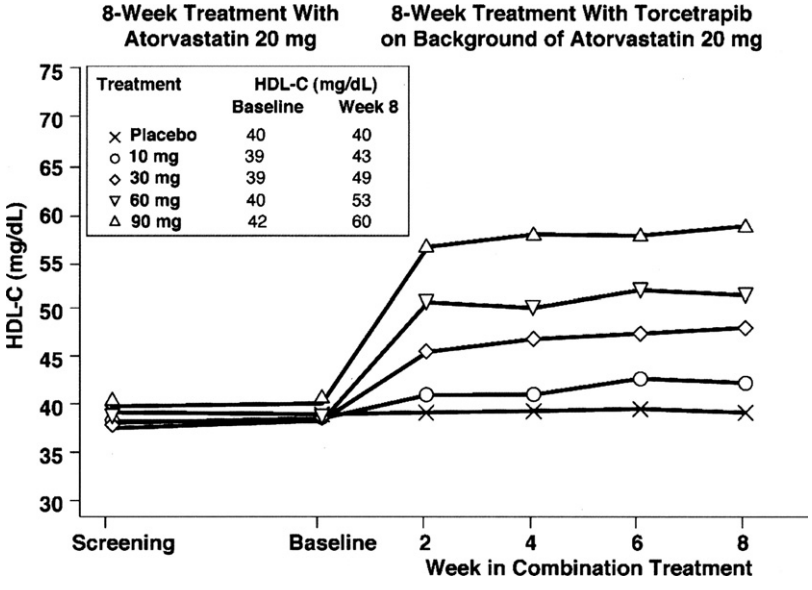

Figure 2. Mean change in high-density lipoprotein cholesterol (HDL-C) over the course of the study—all patients.

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Table 3. Change in Other Lipid Parameters (All Patients Received Background Atorvastatin 20 mg/day)

Mean Values at Baseline and Week 8 (Baseline, Final mg/dl)

Parameter	Placebo	Torcetrapib (mg/day) 10	30	60	90
Lipoproteins					
Apo A-I	132.0, 127.4	134.3, 134.7	131.4, 147.0	130.5, 141.3	136.2, 149.2
Apo A-II	30.5, 29.7	31.1, 32.1	30.1, 33.1	31.3, 33.8	31.4, 33.7
Apo B-100	101.5, 99.2	99.5, 97.6	98.5, 101.2	97.2, 90.2	101.5, 84.6
Non–HDL-C	121.8, 123.7	118.6, 121.5	117.5, 124.7	115.7, 107.2	119.3, 102.8
Ultracentrifugation/precipitation analysis					
HDL-2 cholesterol	11.4, 12.0	11.5, 14.1	11.6, 15.5	10.9, 18.0	12.8, 23.6
HDL-3 cholesterol	28.7, 27.9	27.8, 28.7	27.6, 33.0	28.6, 34.9	29.2, 36.1

Percent Change From Baseline at Week 8 (LS Mean Differences Relative to Placebo Using LOCF Approach)

Parameter	Torcetrapib (mg/day) 10	30	60	90
Lipoproteins				
Apo A-I (95% CI)	4.3 (−2.3, 10.9)	15.2† (8.8, 21.7)	11.6† (4.9, 18.3)	14.8‡ (8.1, 21.5)
Apo A-II (95% CI)	6.4* (0.8, 12.0)	12.1† (6.7, 17.5)	11.3† (5.6, 16.9)	11.0† (5.4, 16.7)
Apo B-100 (95% CI)	−0.1 (−7.8, 7.7)	3.7 (−3.9, 11.2)	−6.3 (−14.2, 1.6)	−14.9† (−22.7, −7.0)
Non–HDL-C (95% CI)	0.8 (−7.5, 9.1)	3.9 (−4.2, 12.0)	−9.8* (−18.3, −1.3)	−16.0† (−24.4, −7.6)
Ultracentrifugation/precipitation analysis				
HDL-2 cholesterol (95% CI)	10.1 (−30.3, 50.5)	26.5 (−13.0, 66.0)	74.2† (33.1, 115.3)	74.1† (32.2, 115.0)
HDL-3 cholesterol (95% CI)	4.5 (−4.1, 13.1)	20.0‡ (11.6, 28.4)	26.3‡ (17.6, 35.0)	27.7‡ (19.1, 36.4)

*$p < 0.05$. †$p < 0.01$. ‡$p \leq 0.0001$.
Abbreviations as in Table 2.

(SD ± 6.0) to 27.9 mg/dl (SD ± 11.2), equivalent to a 94% increase, and from 17.8 (SD ± 6.5) to 36.0 mg/dl (SD ± 16.1), equivalent to a 113% increase, respectively ($p \leq 0.0001$ for both). At the same doses, mean HDL particle size also increased from 8.4 (±0.3) to 8.8 nm (±0.4) and from 8.5 (±0.2) to 9.1 nm (±0.5), respectively ($p \leq 0.0001$ for both).

APO B-RELATED LIPOPROTEINS. At Week 8, torcetrapib on a background of atorvastatin produced moderate but significant decreases in LDL-C levels from baseline (LS mean difference from placebo) at both the 60-mg (−15.7%; $p < 0.01$) and 90-mg (−18.9%; $p < 0.01$) doses (Table 2, Fig. 3). These significant effects on LDL-C lowering were maintained regardless of whether baseline triglyceride levels were low or high; this was not the case in the companion study of patients receiving torcetrapib alone (Table 4). The Apo B-100 levels were decreased in the torcetrapib 60-mg (−6.3%) and 90-mg (−14.9%; $p < 0.01$) treatment groups (Table 3).

The NMR analysis showed a trend toward reduction in the concentration of the small LDL-C subclass. At the

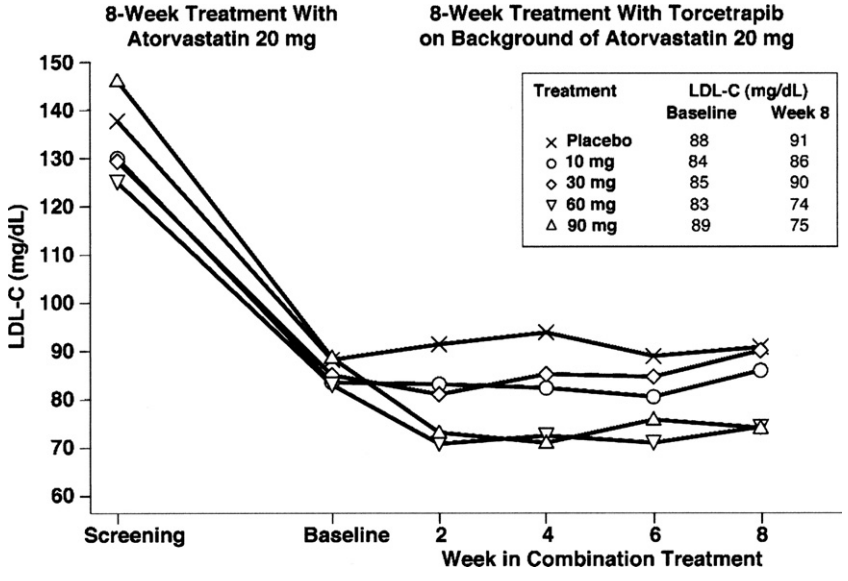

Figure 3. Mean change in low-density lipoprotein cholesterol (LDL-C) over the course of the study—all patients.

Table 4. Effect of Baseline Triglyceride (TG) Levels on Mean Percent Change (95% CI) in LDL-C (LS Mean Difference Relative to Placebo at Week 8, LOCF)

	Torcetrapib (mg/day)			
Companion Study	**10**	**30**	**60**	**90**
TG ≤150 mg/dl	0.8 (−9.5, 11.1)	−2.9 (−14.0, 8.3)	−22.2 (−32.7, −11.6)‡	−32.9 (−44.3, −21.4)‡
n	13	10	12	9
TG >150 mg/dl	−1.5 (−14.1, 11.0)	6.8 (−5.6, 19.2)	0.1 (−12.0, 12.2)	−10.3 (−22.2, 1.5)
n	19	20	22	24
	Torcetrapib (mg/day) Plus Background Atorvastatin 20 mg/day			
Current Study	**10**	**30**	**60**	**90**
TG ≤150 mg/dl	−8.1 (−24.5, 8.2)	−3.8 (−18.9, 11.4)	−17.9 (−34.3, −1.6)*	−20.0 (−34.9, −5.2)†
n	14	19	14	21
TG >150 mg/dl	7.3 (−3.8, 18.4)	9.7 (−1.5, 20.9)	−13.6 (−25.1, −2.2)*	−17.0 (−30.1, −3.8)*
n	20	18	17	11

*$p < 0.05$; †$p < 0.01$; ‡$p \leq 0.0001$.
Abbreviations as in Table 2.

60-mg and 90-mg doses of torcetrapib, small LDL (18.3 to 19.7 nm) decreased from 26.0 (SD ± 34.3) to 13.3 mg/dl (SD ± 14.8) and from 25.1 (SD ± 31.9) to 13.9 mg/dl (SD ± 31.5), respectively ($p = 0.13$, not significant for both). The NMR spectroscopy showed that LDL particle size was increased dose dependently. Torcetrapib 60 mg and 90 mg increased mean LDL particle size from 20.4 (±0.7) to 21.0 nm (±0.5) and from 20.5 (±0.6) to 21.2 nm (±0.7), respectively ($p \leq 0.0001$ for both).

There was a −24.4% decrease from baseline in VLDL-C at Week 8 with torcetrapib 90 mg ($p = 0.0128$). The VLDL triglyceride levels did not show any consistent dose-related pattern.

Non-HDL cholesterol levels were significantly decreased from baseline in the torcetrapib 60-mg and 90-mg groups ($p < 0.05$ and $p < 0.01$, respectively) (Table 3).

LIPID RATIOS, TOTAL CHOLESTEROL, AND TRIGLYCERIDES. At Week 8, torcetrapib on a background of atorvastatin produced dose-related decreases in the LDL-C/HDL-C ratio of up to −40% ($p < 0.01$ for doses of 30 mg and above), consistent with the observed increases in HDL-C levels and decreases in LDL-C levels (Table 2, Fig. 4). The final LDL-C/HDL-C ratio in the torcetrapib 60-mg and 90-mg groups was ≤1.5. Similarly, at Week 8, there were dose-related decreases in the apo B-100/apo A-I ratio (Table 2). No consistent dose-dependent effects on the levels of total cholesterol or triglycerides were observed (Table 2).

Safety and tolerability. Administering torcetrapib on a background of atorvastatin did not seem to alter the safety profile of torcetrapib from that observed in a study of torcetrapib monotherapy (see accompanying article, pages 1774–1781 in this issue of the *Journal*).

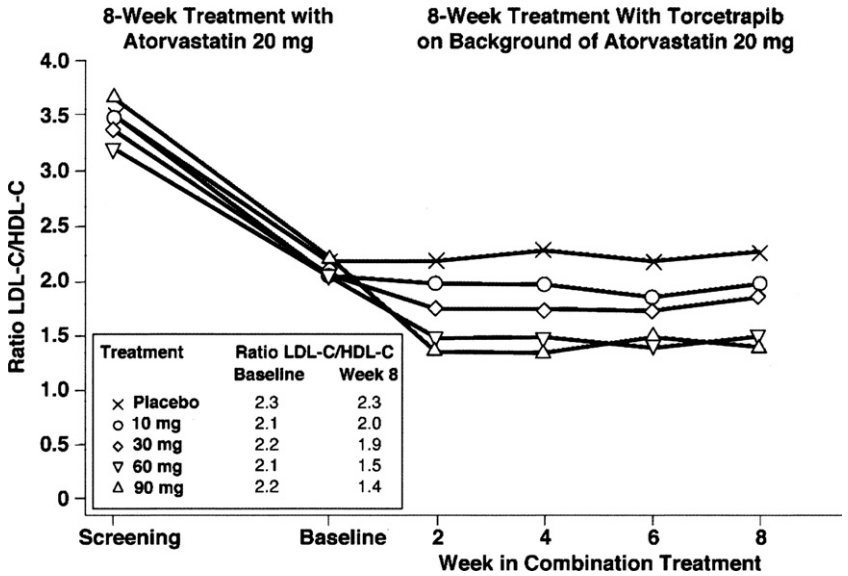

Figure 4. Change in LDL-C/HDL-C ratio over the course of the study—all patients. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

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Table 5. Summary of Safety—Number of Patients (%) (All Patients Received Background Atorvastatin 20 mg/day)

		Torcetrapib (mg/day)			
	Placebo (n = 37)	10 (n = 34)	30 (n = 39)	60 (n = 31)	90 (n = 33)
Treatment-related withdrawals	0 (0)	0 (0)	4 (10)*	0 (0)	1 (3)*
Subjects with AEs					
All-causality	24 (65)	13 (38)	24 (62)	12 (39)	20 (61)
Treatment-related	7 (19)	4 (12)	13 (33)	4 (13)	8 (24)
Serious AEs					
All-causality	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Treatment-related	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	(n = 37)	(n = 34)	(n = 37)	(n = 31)	(n = 33)
Clinical laboratory tests					
ALT/AST >3 × ULN (with or without abnormal baseline†)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
CK >10 × ULN	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)

*One patient in the 30-mg group and the patient in the 90-mg group only temporarily discontinued from treatment and completed the study. †Baseline values are the measurements taken at the end of the atorvastatin run-in period.
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; ULN = upper limit of normal.

Across the investigated dose range, torcetrapib was generally well tolerated. Treatment-related discontinuations from the study were rare, consisting of 4 patients receiving torcetrapib 30 mg and 1 patient receiving torcetrapib 90 mg (Table 5). Two patients had a temporary discontinuation of treatment. The AEs leading to treatment-related discontinuations included lightheadedness, eye pain, headache, fever, diarrhea, night sweats, and intermittent epigastric pain.

The incidence of all-causality and treatment-related AEs was similar across placebo and torcetrapib groups with no evidence of a dose-related response (Table 5). Flatulence and nausea were the most frequently reported treatment-related AEs. Most AEs were mild or moderate in nature. There were no treatment-related serious AEs in this study.

Laboratory test abnormalities showed no dose-related trends. Only 1 patient in the torcetrapib 90-mg group showed elevated liver transaminase levels (AST/ALT > 3 × the upper limit of normal [ULN]), and that patient had a baseline level >3 × ULN before randomization. One patient on torcetrapib 90 mg had a creatine kinase level >10 × ULN (Table 5), which was considered a result of exercise. No muscle symptoms were reported.

Changes from baseline in systolic and diastolic blood pressure (SBP and DBP) at follow-up visits were highly variable in both placebo- and torcetrapib-treated patients, with no apparent dose-dependent response (Fig. 5). Mean SBP changes over the course of the study ranged from −0.2 mm Hg (torcetrapib 10-mg group) to 2.2 mm Hg (torcetrapib 60-mg group), with only the change in the 60-mg group achieving statistical significance (Table 6). Mean DBP changes ranged from −0.8 mm Hg (placebo group) to 1.1 mm Hg (torcetrapib 90-mg group), with no significant change in any group (Table 6).

Of the patients receiving torcetrapib on a background of atorvastatin, 2.9% (4 of 137) showed significant elevations in blood pressure defined as: 1) SBP ≥15 mm Hg or DBP ≥10 mm Hg from baseline at 3 consecutive visits, or 2) SBP ≥180 mm Hg with a ≥20 mm Hg change from baseline or DBP ≥105 mm Hg with a ≥15 mm Hg change from baseline at a single visit. No patient was permanently discontinued from the study because of elevated blood pressure.

DISCUSSION

In an accompanying article (see pages 1774–1781 in this issue of the *Journal*), we showed that torcetrapib produces a

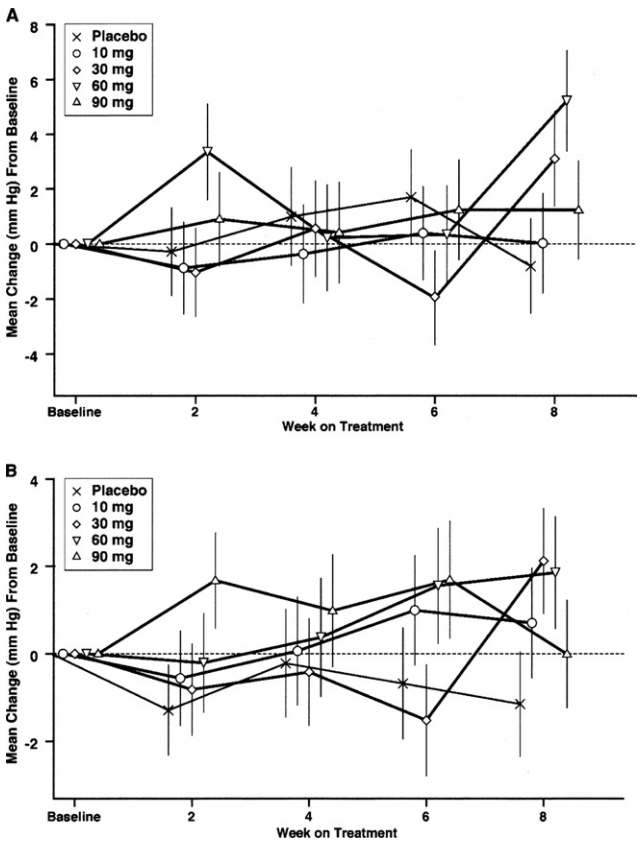

Figure 5. Least-squares mean change in systolic **(A)** and diastolic **(B)** blood pressure over the course of the study.

Table 6. Longitudinal Analysis of Changes in Blood Pressure: Average of All Follow-Up Measures Over the Course of the Study (All Patients, Observed Cases; All Patients Received Background Atorvastatin 20 mg/day)

		Torcetrapib (mg/day)			
	Placebo (n = 37)	10 (n = 34)	30 (n = 38)	60 (n = 31)	90 (n = 33)
Systolic blood pressure					
Least-squares mean change	0.39	−0.20	0.09	2.22	0.94
95% confidence interval	−1.29–2.07	−1.91–1.51	−1.58–1.76	0.43–4.02	−0.82–2.70
Diastolic blood pressure					
Least-squares mean change	−0.84	0.28	−0.20	0.87	1.09
95% confidence interval	−2.00–0.32	−0.90–1.46	−1.36–0.96	−0.37–2.12	−0.12–2.30

range of beneficial effects on lipoproteins when administered to patients with low levels of HDL-C. The data that we present here from an equivalent group of patients who were also receiving atorvastatin 20 mg show a similar pattern of beneficial lipoprotein changes. Specifically, there were substantial dose-dependent increases in HDL-C of up to 40.2% with the 90-mg dose, modest decreases in LDL-C with both the 60-mg (−15.7%) and 90-mg (−18.9%) doses, increases in HDL and LDL particle size with all doses, and a reduction in the LDL-C/HDL-C ratio to ≤1.5 with the 60-mg and 90-mg doses. Torcetrapib plus background atorvastatin also produced a similar pattern of changes in apo A-I, A-II, and B-100 as with torcetrapib alone. Of note, particularly with respect to LDL-C, changes in lipoprotein levels in this study are additive to those achieved with atorvastatin monotherapy.

Interestingly, there was no apparent loss of LDL-C reduction in this study when baseline triglycerides were high, unlike that observed in the companion study of torcetrapib monotherapy. As discussed in the accompanying article, one possible explanation for this observation may be as follows. In the metabolic setting of high triglycerides, the combination of compositional changes in VLDL-1 and CETP inhibition may lead to accelerated conversion of VLDL to LDL via lipoprotein lipase, which may nullify the effect of torcetrapib on LDL-C levels. However, with statin therapy, up-regulation of LDL receptors may help to reduce accumulation of LDL-C, thereby ensuring that the effect of torcetrapib in patients with hypertriglyceridemia is more consistent with that observed in patients who are normotriglyceridemic. These findings suggest that an apparent limitation of CETP inhibitor monotherapy is overcome by concomitant statin therapy.

To date, the only other data pertaining to the addition of a CETP inhibitor to statin therapy comes from a study published by Kuivenhoven et al. (13). In this study, 4 weeks of treatment with JTT-705 600 mg in patients receiving background pravastatin 40 mg resulted in a 30% decrease in CETP activity, a 28% increase in HDL-C, and a 5% decrease in LDL-C.

Regarding safety, this study shows that torcetrapib is well tolerated when administered with atorvastatin. Discontinuations from treatment were rare, and there were no dose-related trends in the incidences of AEs. Furthermore, torcetrapib with atorvastatin had no additional impact on the slight increases in blood pressure that were observed in the study of torcetrapib alone (see accompanying article, pages 1774–1781 in this issue of the *Journal*).

There is overwhelming evidence showing that lowering LDL-C with statins is associated with significant cardiovascular benefits (3), and current guidelines for CVD prevention maintain a focus on LDL-C as the primary risk factor for modification (1,2). Indeed, the National Cholesterol Education Program Adult Treatment Panel recently published an update to their latest guidelines, in which optional therapeutic LDL-C goals of <70 mg/dl for very high-risk patients and <100 mg/dl for high-risk patients were suggested. Yet, given that there is substantial potential for further risk reduction in statin-treated patients, there is a clear need for more comprehensive lipid management targeting other elements of an atherogenic lipid profile. The results from this study show that by combining LDL- and HDL-targeted therapies, statin-eligible patients can achieve a lipid profile consistent with even lower cardiovascular risk. Comparing the results from this study with those from the companion study of torcetrapib monotherapy, it is evident that 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibition with atorvastatin and CETP inhibition with torcetrapib have complementary actions, resulting in more robust LDL-C lowering and LDL-C/HDL-C ratios approaching 1.0. Ultimately, large-scale, randomized clinical trials are required to determine whether the addition of torcetrapib to atorvastatin will prove to have a greater impact on atherosclerosis than atorvastatin alone. Several such studies are underway, including vascular imaging studies using ultrasound to measure carotid artery intima-media thickness and coronary atheroma volume (14–16).

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